综述

紧密连接蛋白-1功能研究进展

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摘要 紧密连接蛋白-1(claudin-1)作为紧密连接的主要组成蛋白之一, 位于人染色体3q28区域, 分子量为22.7 kDa, 由211个氨基酸残基组成。Claudin-1在肠、食管、肺等组织中均有表达, 尤其在肝脏、肾脏、皮肤等组织中表达较高。Claudin-1在细胞中主要定位于细胞膜、细胞核、细胞质以及双细胞的紧密连接等。Claudin-1是诱导上皮–间质转化(epithelial-mesenchymal transition, EMT)发生的重要蛋白之一, 参与肿瘤细胞迁移与侵袭, 并介导抗凋亡及细胞增殖。Claudin-1在炎症性肠病、肿瘤、哮喘等疾病的发生发展中扮演重要角色。故该文从claudin-1的分子生物学特性、组织表达及亚细胞定位、参与的重要生物学过程及相关疾病方面进行了综述。

关键词 claudin-1; 上皮间质转化; 迁移; 增殖

Research Advances in the Function of Claudin-1

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Abstract Claudin-1 is one of the main components of tight junctions. It is located in the region of human chromosome 3q28. It has a molecular weight of 22.7 kDa and is composed of 211 amino acids. Claudin-1 expresses in intestine, esophagus, lung and other tissues, especially in liver, kidney, and skin. It is mainly located in the cell membrane, nucleus, cytoplasm, and the tight junction between two cells. Claudin-1 is one of the important proteins that induces the occurrence of EMT (epithelial-mesenchymal transition), which is involved in tumor cell migration and invasion and mediates anti-apoptosis and cell proliferation. It plays an important role in the occurrence and development of inflammatory bowel disease, tumors, and asthma. Therefore, this article reviews the molecular biological characteristics, tissue expression and subcellular localization, important biological processes and diseases correlated with claudin-1.

Keywords claudin-1; epithelial-mesenchymal transition; migration; proliferation

紧密连接蛋白家族(claudins)是一个庞大的膜蛋白家族, 最早在鸡肝中被发现, 目前在哺乳动物中已发现27个紧密连接蛋白家族成员[1]。Claudins是上皮细胞、间皮细胞、周围神经细胞以及内皮细胞间

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的紧密连接(tight junction, TJ)的关键成分, 其功能主要包括参与调节细胞外通透性、细胞极性、分化和增殖、迁移和凋亡, 介导细胞信号传导等[2]。作为紧密连接蛋白家族的重要成员, claudin-1是紧密连接的主要组成蛋白之一[3]。研究发现, 敲除claudin-1基因后, 小鼠因严重的屏障功能受损导致表皮脱水而死亡[4]。组织特异性敲除claudin-1的研究表明, 人角质形成细胞中claudin-1缺失表达会引起划痕愈合明显受损、迁移延迟、增殖减少等[5]。如果claudin-1基因发生突变, 儿童可表现为皮肤结垢、进行性瘢痕和胆管阻塞, 即新生儿硬化性胆管炎伴鱼鳞病[6]。此外, 进一步研究发现, claudin-1的异常表达可导致上皮细胞、内皮细胞和间皮细胞的结构破坏和功能受损[7]。因此, claudin-1可能在多种疾病的发生发展中扮演重要角色。故本文准备从claudin-1的分子生物学特性、组织表达及亚细胞定位、参与的重要生物学过程及相关疾病4个方面进行综述。

1 Claudin-1蛋白的分子生物学特性

Claudin-1又被称为衰老相关的上皮膜蛋白-1(senescence-associated epithelial membrane protein-1)[8]。Claudin-1位于人染色体3q28区域, 分子量为22.7 kDa, 由211个氨基酸残基组成[9]。Claudin-1含有4个跨膜结构域、2个胞外环[ECL1(the first extra cellular loop)和ECL2(the second extra cellular loop)]、1个细胞质内环以及位于细胞质中的NH_2-和COOH-端, 相邻细胞间通过外环以“拉链”状结构封闭[9](图1)。ECL1由大约50个氨基酸组成, 包括一组高度保守的残基W-GLW-C-C, 其氨基酸组成影响细胞旁电荷选择性, 决定细胞旁孔的性质[10]。ECL1含有2个分别位于54位和64位的半胱氨酸, 这2个半胱氨酸形成一个分子内二硫键桥, 具有很强的保守性, 决定整个ECL1的结合行为, 对claudin-1的封闭功能至关重要[11]。而ECL2相对较小, 含有16~33个氨基酸残基, 介导细胞内和相邻细胞间的claudin-claudin相互作用[12], 并通过调控细胞旁空间的电荷和大小选择特性, 对细胞外的水和溶质的流动、其他细胞的转位起到屏障的作用[13]。Claudin-1的C-端是以缬氨酸结尾的COOH-端, 长度为21~63个氨基酸残基, 含有结合PDZ结构域的结构基序, 能与闭锁小带蛋白-1(zonula occludens protein-1, ZO-1)、多PDZ域蛋白1(multi-PDZ domain protein 1, MUPP1)等结合形成紧密连接, 最终实现上皮屏障功能[14]。

2 Claudin-1蛋白的组织表达及亚细胞定位

Claudin-1广泛表达于多种细胞与组织中[15], 在肠、食管、肺等组织中均有表达, 尤其在肝脏、肾脏、皮肤等组织中表达较高(https://www.genecards.org)(图2)。Claudin-1定位于细胞膜、细胞核、细胞质以及双细胞的紧密连接等[16]。研究发现, 在生理情况下, claudin-1在动脉平滑肌细胞中定位于细胞核和

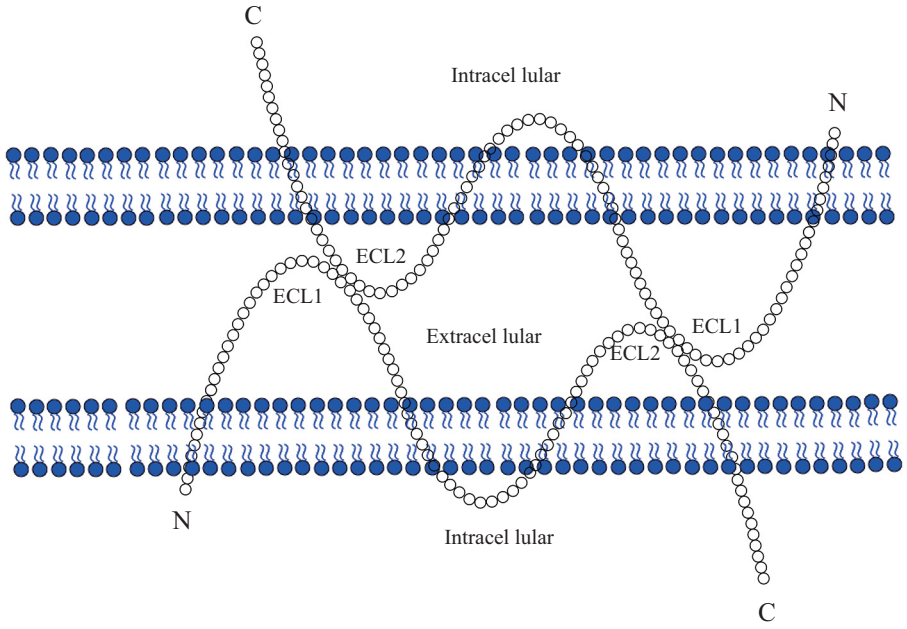

图1 Claudin-1的形态及结构

Fig.1 Morphology and structure of claudin-1

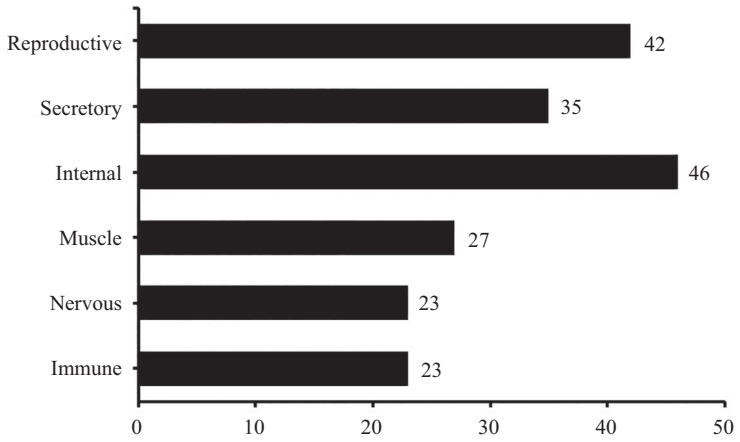

图2 正常组织中的claudin-1基因表达(来自BioGPS数据库)

Fig.2 Claudin-1 gene expression in normal tissues (from BioGPS database)

细胞质, 在上皮细胞、成纤维细胞中定位于细胞表面[17]。此外, claudin-1在朗格汉斯细胞和淋巴结树突状细胞中均有表达, 并促进它们的黏附和迁移[18]。而在病理状态下, claudin-1会出现异常定位, 如在结肠癌中claudin-1表达增加, 同时还会出现从细胞膜到细胞核和细胞质的异常定位[19]。在磷酸酶调节亚基敲除的细胞中, claudin-1由质膜转移至细胞质, 而抑制c-Jun磷酸化可恢复claudin-1的屏障功能和质膜定位[20]。

3 Claudin-1蛋白参与的重要生物学过程

3.1 介导上皮间质转化(epithelial-mesenchymal transition, EMT)

Claudin-1是诱导EMT发生的重要蛋白之一。研究发现, claudin-1主要通过非受体Abelson酪氨酸激酶–细胞外调节蛋白激酶(Abelson tyrosine kinase-extracellular regulated protein kinases, c-Abl-ERK)信号通路和β-连环蛋白(beta-catenin, β-catenin)/T细胞因子(T cell factor, TCF)/淋巴增强因子(lymphoid enhancer factor, LEF)通路诱导EMT的发生[21]。过表达的claudin-1通过c-Abl-ERK信号通路进而激活基质金属蛋白酶(matrix metalloproteinases, MMPs)[22], 被激活的MMPs会破坏细胞外基质进而诱导EMT的发生[22]。Claudin-1还是已知的β-catenin/TCF/LEF依赖的转录监管目标, 参与β-catenin/TCF/LEF信号通路[23]。在生理情况下, β-catenin与钙黏蛋白(E-cadherin)和肌动蛋白骨架(actin skeleton)在细胞间连接处形成复合物并形成屏障[24]。而过表达的claudin-1诱导β-catenin磷酸化使β-catenin/E-cadherin/actin复合物解离, 导致EMT的发生[25]。进一步研究发现, EMT的发生可能引起纤维化和癌症等病理过程[26]。因此, 在炎症性肠病(inflammatory bowel disease, IBD)肠纤维化及肿瘤等相关疾病中, claudin-1诱导EMT发生的生物学机制得到了越来越多的关注, 通过了解其机制为疾病的治疗提供可靠依据。

3.2 参与细胞迁移与侵袭

Claudin-1通过降低细胞黏附分子表达、激活MMPs等生物学过程, 导致上皮细胞失去细胞极性和黏附周围细胞的能力, 进而向间充质细胞分化[27], 从而在肿瘤细胞迁移和侵袭等过程中发挥重要作用[21]。在结肠癌中, claudin-1过表达抑制了E-cadherin的表达, 从而促进了细胞的迁移和侵袭[28]。此外, 在某些类型癌症中, 过表达的claudin-1可以激活MMPs, 而被激活的MMPs会破坏细胞外基质, 帮助转化细胞侵袭或迁移[29]。同时, claudin-1的启动子区Sp1转录因子活性升高也能介导MMPs在人子宫内膜癌细胞侵袭中的作用。然而claudin-1与细胞迁移的关系也高度依赖于肿瘤类型。虽然在多数肿瘤中过表达的claudin-1促进肿瘤细胞的迁移, 但相反地, 在肺癌中claudin-1的过表达能够抑制细胞的迁移[30]。因此, claudin-1在肿瘤的发生发展过程中起着重要的调节作用。

3.3 介导抗凋亡及细胞增殖

过表达的claudin-1还能介导细胞的抗凋亡能力进而诱导细胞的增殖, 导致疾病的恶化[17]。近期研究发现, claudin-1可保护细胞不受脱落凋亡的干扰[31]。脱落凋亡是细胞脱离细胞外基质后发生的一种特殊形式的凋亡, 是维持组织稳态和发育的关键机制。受claudin-1保护的细胞可发生脱落凋亡失效, 在悬浮液条件下存活或在异位部位增殖, 这一生物学过程被认为有

助于癌细胞在其他器官中形成转移增殖，促进癌症的发展[32]。在呼吸系统疾病中，肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)可通过核因子κB(nuclear factor kappa-B, NF-κB)信号通路诱导人气道平滑肌中claudin-1的表达，而过表达的claudin-1通过ERK1/2的磷酸化和激活促进气道平滑肌的增殖[33]。因此，claudin-1介导的抗细胞凋亡及促进细胞增殖的功能在肿瘤的转移中起重要作用，同样在气道平滑肌增殖等增生性疾病中至关重要。

4 Claudin-1参与的通路及上下游分子

Claudin-1参与多条信号传导通路，现已被确定为β-catenin/TCF信号通路的靶点[34]。在β-catenin/TCF信号通路中，生长因子EGF、Snail-1、TGF-β等可上调claudin-1的表达，进而招募MMP-2并促进其激活，参与细胞侵袭和转移[19]。Claudin-1还可参与c-Abl-ERK信号通路，在此通路中claudin-1过表达可诱导EMT调节转录因子Snail家族转录因子2(Snail family transcriptional repressor 2, Slug)和E盒结合锌指蛋白1(zinc finger E-box-binding 1, Zeb1)的表达，从而抑制E-cadherin、β-catenin的表达，增强N-cadherin和Vimentin的表达，使细胞黏附丧失、细胞运动增强，而抑制c-Abl或ERK可明显减弱claudin-1诱导的EMT，使得N-cadherin、E-cadherin表达模式发生逆转，并使细胞恢复正常的运动能力[22]。然而除上述通路外，claudin-1还可参与其他通路(表1)。

5 Claudin-1参与的疾病

5.1 IBD的发生及纤维化肠狭窄

IBD的结肠上皮屏障功能障碍已成为其发病过程中的一个关键特征[38]。而存在于肠上皮细胞间的紧密连接结构可调节细胞旁通透性[39]。Claudin-1广泛表达于肠上皮细胞，以其屏障形成能力而为人所知，并被认为对紧密连接的完整性具有重要作用[40]。Claudin-1表达降低可导致紧密连接的数量和复杂性的降低，进而引起肠上皮屏障功能减弱[41]。例如，研究发现TNF-α等细胞因子能改变claudin-1的表达与分布[42]。异常表达与分布的claudin-1导致紧密连接链断裂形成孔洞及泄漏途径，使离子及大的溶质穿过细胞间隙损伤肠道，从而降低肠道的屏障功能[43]。Claudin-1还可与MMPs结合并诱导其活化，增加了Notch受体的蛋白水解，调节Notch靶基因的转录，进而调节细胞的分化，决定细胞命运，从而影响结肠稳态。当IBD持续的肠损伤存在时，炎症相关因子诱导紧密连接蛋白claudin-1的表达，进而激活Wnt/β-catenin信号通路诱导EMT发生以期修复损伤部位，然而诱导的EMT过程可导致IBD肠纤维化的发生[44]。过表达的claudin-1还能通过上调MMPs和ERK1/2激活Notch信号通路，诱导局部间充质细胞增殖，并通过EMT过程导致腔径减小、肠道狭窄和阻塞[45]。

5.2 肿瘤

越来越多的证据表明，claudin-1在肿瘤中除连接功能外还具有其他的功能，如它的过度表达或错误

表1 Claudin-1参与的通路及上下游分子

Table 1 Pathways and upstream and downstream molecules correlated with claudin-1

通路 Pathways	上游分子 Upstream molecules	下游分子 Downstream molecules	参考文献 Reference
β-catenin/TCF signaling pathway	Snail-1, EGF, TGF-β, PKA, PKC, β-catenin	E-cadherin, MMP-2	[34,19]
MEK/ERK Pathway	MEK, ERK1/2, TNF-α, IL-6, cecropin A, CDX-2, IGF-1, PMAPK, EGF	F-actin, ZOs	[35-36]
PI3K/Akt signaling pathway	Akt, PI3K, EGF, PGE2, COX-1, COX-2	F-actin, ZOs	[35,37]
c-Abl-ERK signaling pathway	c-Abl, ERK	Slug, Zeb1, E-cadherin, β-catenin, N-cadherin, Vimentin	[22]
EGFR/Akt/p38/ERK signaling pathway	EGFR, Akt, ERK, NF-κB	E-cadherin, β-catenin, N-cadherin, Vimentin	[21]

EGF: 表皮生长因子; TGF-β: 转化生长因子-β; PKA: 蛋白激酶A; PKC: 蛋白激酶C; MEK: 丝裂原活化蛋白激酶; CDX-2: 尾侧型同源转录因子-2, IGF-1: 胰岛素样生长因子-1; Akt: 苏氨酸蛋白激酶; PI3K: 磷脂酰肌醇-3-激酶; PGE2: 前列腺素E2; COX: 环氧酶。

EGF: epidermal growth factor; TGF-β: transforming growth factor-beta; PKA: protein kinase A; PKC: protein kinase C; MEK: mitogen-activated protein kinase; CDX-2: caudal type homeobox transcription factor-2; IGF-1: insulin like growth factor-1; Akt: threonine protein kinase; PI3K: phosphatidylinositol 3-kinase; PGE2: prostaglandin E2; COX: cyclooxygenase.

表2 常见疾病与claudin-1的关系

Table 2 Relationships between claudin-1 and common diseases

疾病 Disease	Claudin-1状态 The state of claudin-1	检测方法 Detection method	样品来源 Sample source	参考文献 Reference
Colon cancer	Overexpression>150%, localized at the nucleus and cytoplasm	WB, IF	Rectal cancer cells	[53]
Breast cancer	Overexpression>300%, located at the cell-cell junction, cell periphery	CO-IP, PCR, WB, IF	Breast cancer cell	[46]
Asthma	Overexpression>200%, localized at the nucleus and cytoplasm	WB, IHC, RT-PCR	Bronchial and airway smooth muscle cells	[17]
Mild to moderate crohn's disease	Low expression<50%, located at the cell-cell junction	WB, IF	Colonic epithelial cells	[54]
Delayed wound healing	Low expression<20%, loss of trauma margin	WB, IF	Skin tissue	[5]
Neonatal sclerosing cholangitis with ichthyosis	Claudin-1 gene exon 2-bp deletion	WB, IHC	Hepatic tissue	[55]

CO-IP: 免疫共沉淀; PCR: 聚合酶链式反应; WB: 免疫印迹; IF: 免疫荧光; RT-PCR: 逆转录PCR; IHC: 免疫组织化学。

CO-IP: co-immunoprecipitation; PCR: polymerase chain reaction; WB: Western blot; IF: immunofluorescence; RT-PCR: reverse transcription PCR; IHC: immunohistochemistry.

定位可通过增强细胞存活、侵袭和转移而导致癌症恶化[46]。在结肠癌的细胞转化、肿瘤生长和转移中, claudin-1起着重要的调节作用[12]。Claudin-1的PDZ结构域通过与ZO-2相互作用将蛋白从细胞膜转移至细胞核, 导致其异常定位, 促进肿瘤的发生发展[43]。且过表达的claudin-1能增加MMP-2和MMP-9的活性, 诱导EMT的发生, 增强肿瘤细胞在体外的侵袭性, 并促进肿瘤的转化[19]。研究发现, 在结肠癌中过表达的claudin-1还能调节β-catenin/TCF的表达和钙黏蛋白信号通路, 进而调控结肠癌细胞的脱落凋亡, 从而影响结肠癌的侵袭和转移[28]。同样地, claudin-1在其他多种肿瘤中过度表达可促进肿瘤的发生发展, 如在侵袭性乳腺导管癌中, ADAM15(a disintegrin and metalloproteinase 15)通过上调下游的claudin-1诱导肿瘤细胞的侵袭增殖, 影响疾病的预后[46]。在宫颈癌中, claudin-1通过诱导EMT的发生促进宫颈癌细胞的侵袭和转移, 进而影响疾病发展[47]。此外, 在卵巢癌渗出液中claudin-1水平的升高能够降低卵巢癌患者的存活率[48]。因此, claudin-1在肿瘤的发生发展中扮演重要角色。

5.3 其他临床疾病

Claudin-1的异常定位及表达同样会导致呼吸系统疾病的发生发展。研究发现, claudin-1在肺动脉平滑肌细胞中定位于细胞核和细胞质, 与细胞内信号机制密切相关[22]。在野百合碱诱导的肺动脉高压老鼠的肺血管平滑肌中, TNF-α可通过NF-κB信号通路来诱导claudin-1的表达[49]。而被激活的claudin-1可通过激活ERK1/2促进气道平滑肌细胞增殖, 从而促进哮喘患者气道重组[17,33]。Claudin-1还广泛表达于气道上皮中, 可调节相邻上皮细胞之间的黏附[50]。在急性肺损伤中, 蛋白酶D3通过下调claudin-1的表达, 增加气道上皮通透性, 破坏上皮屏障功能[51]。而胸腺基质淋巴细胞生成素及过氧化物酶体增殖物激活受体可增加claudin-1的表达, 以提高气道上皮的紧密度, 保护其屏障功能[52]。除上述由claudin-1的异常表达导致的疾病外, claudin-1还可参与多种疾病的发生发展(表2)。

6 结语

近年来, 越来越多的研究发现, claudin-1作为紧密连接蛋白家族的重要成员之一, 不仅仅在细胞间的紧密连接处起到屏障功能, 同时还在诱导EMT的发生, 参与细胞迁移及侵袭, 诱导抗凋亡及细胞增殖等方面发挥着重要作用。Claudin-1通过不同的通路及机制发挥上述作用, 我们猜测调控claudin-1的上下游分子表达情况可能起到抑制claudin-1诱导的EMT、细胞迁移及侵袭、抗凋亡及细胞增殖等作用, 从而起到预防IBD、肿瘤等与其相关的疾病的发生发展的作用。随着人们越来越关注claudin-1的

异常定位在疾病中的作用, 更多的调控机制将被挖掘出来。这些机制的发现将为IBD、肿瘤等疾病的研究、新药物及治疗方法的研发提供新思路, 为将来claudin-1在临床上的应用提供更多的证据支持。

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